Prognostication in Pulmonary Arterial Hypertension and Use of Current Risk Prediction Models

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Significant therapeutic advances in the field of pulmonary arterial hypertension (PAH), increased awareness and diagnosis, and changing patient demographics in the contemporary era have facilitated the development of better prognostic tools for predicting survival. However, overall patient outcomes remain poor, and measurement of most prognostic factors still occurs at the time of initial PAH diagnosis or enrollment into clinical trials. Treatment of PAH patients requires an individualized approach based on disease severity and burden of risk factors to improve patient outcomes. This article will focus on the use of risk prediction models to map and target individual disease trajectories to avoid future morbid and mortal events.

Since the time of the National Institutes of Health (NIH) registry conducted in the 1980s of incident pulmonary arterial hypertension (PAH) cases reporting a median survival of 2.8 years after diagnosis,[1] significant therapeutic advances in the field, increased awareness and diagnosis, and changing demographics of PAH patients in the contemporary era have facilitated the development of better prognostic tools for predicting survival. One-year survival in the NIH registry before modern therapies existed was a sobering 67%, compared to the 93% 1-year survival estimate of incident PAH cases from US REVEAL (Registry to Evaluate Early and Long-term PAH Disease Management) from 2006-2009 (Figure 1).[2] The French PAH registry, which enrolled patients over a 1-year period from 2002-2003, estimated a 1- and 3-year survival of 82.9% and 58.2% respectively.[3] The NIH registry is no longer relevant for discussion in the current era, but it serves as an important reference for the natural history of untreated PAH patients. Despite superior survival compared with the NIH registry, overall patient outcomes remain poor, and measurement of most prognostic factors still occurs at the time of initial PAH diagnosis or enrollment into clinical trials, when referral and treatment delays may have substantially affected disease progression.[4] We now appreciate that treatment of PAH patients requires an individualized approach based on disease severity and burden of risk factors to improve patient outcomes.[5] Clinical experts are increasingly utilizing risk prediction models for prognosticating pulmonary hypertension (PH) groups and the individual patient both at time of diagnosis and in a serial fashion. With serial risk prediction, individual disease trajectories could be mapped and targeted with timely treatment interventions to avoid future morbid and mortal events. Additionally, the field now desires to prioritize treatment goals associated with long-term outcomes rather than rely on short-term functional changes (ie, 6-minute walk distance or 6MWD) that may not meaningfully translate into improved survival.

PROGNOSIS ACCORDING TO AGE, SEX, AND ETIOLOGY

It is clear from contemporary registry data that the phenotype of patients diagnosed with PAH over the last few decades has changed. While the mean age of patients with idiopathic PAH (IPAH) in the NIH registry was 36 ± 15 years,[1] we now recognize a shift in conjunction with an aging US population, where larger numbers of elderly patients are being diagnosed with PAH—at a mean age of 50 ± 14 years by current registry data (in REVEAL and the French registry). Older patients bring with them more advanced stages of the disease, lower age-related exercise capacity, and multiple comorbidities that impact outcomes, treatment decisions, and consideration for advanced therapies, as well as tolerability to aggressive pharmacotherapy. Not surprisingly, older patients have worse survival compared with younger patients despite the overall improved survival rates in the modern registries.

Female predominance for this disease is widely accepted and appears to have increased over time. Female patients now comprise up to 70% to 80% of registry participants with a 4.1:1 female/male ratio in REVEAL, compared with 63% of women and a 1.7:1 female/male ratio in the NIH registry.[6] The majority of patients with IPAH and connective-tissue disease-associated PAH in REVEAL are women (80% and 90%, respectively). Female sex has been associated with a survival advantage compared to men and likely accounts for some of the striking gender predominance in prevalent cases. The overwhelming disease burden yet survival benefit conferred upon women requires further mechanistic study, but may be partly explained by the role of sex hormones in the pathogenesis of PAH and by beneficial right ventricular (RV) adaption and sex differences in treatment response.[7]

In contrast to age and sex, etiologies of PAH and prognosis therein affected has not appreciably changed. The same relative proportions of etiologies have been reported in the REVEAL registry

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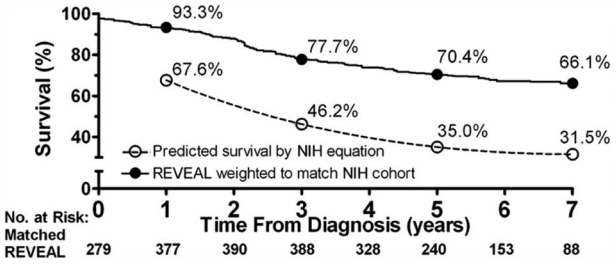

Figure 1: Survival from time of diagnostic RHC in the REVEAL cohort compared to the estimated survival in the historical NIH cohort (matched for age, sex, and mPAP). Median contemporary survival improved to greater than 7 years in the REVEAL registry, compared with a dismal median survival of 2.8 years in "untreated" patients by the NIH registry. Reproduced with permission from the American College of Chest Physicians. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. *Chest.* 2012;142(2):448-456.

from 2006-2009 as were reported in the earlier US Pulmonary Hypertension Connection (PHC) registry from 1982-2006. Prognosis for patients with scleroderma-associated PH unfortunately remains inferior compared to other PAH subgroups, with 30% 1-year mortality in scleroderma PH vs 15% in IPAH.[8] Recent data indicate that contemporary survival in scleroderma PH patients has improved compared with historical controls, and early detection screening programs prior to symptom onset results in significantly better outcomes for these patients.[9]

Human immunodeficiency virus (HIV)-associated PAH and IPAH share similar histopathological characteristics and survival despite a younger age at diagnosis in the HIV subgroup.[10] The prevalence of HIV-PAH is estimated at 0.5% and does not appear to have changed over recent decades.[11] Prior to highly active antiretroviral therapy and PH-specific drugs, HIV-PAH patients had an extremely poor outcome, with 1-year mortality of 50%. Current survival rates for patients with HIV-PAH has improved to 88% at 1 year, and up to 20% of patients experience sustained normalization in hemodynamics with PAH treatment.[12] PAH associated with congenital heart disease (CHD) will likely increase in prevalence, due to the increasing numbers of children with complex and/or repaired CHD who are surviving to adulthood. Despite the negative impact of concomitant PAH in CHD, the natural history of such patients remains favorable and is likely accounted for by their relative youth and better RV adaptation.

Prognosis According to Hemodynamics, 6MWD, and Biomarkers

As RV function is the key determinant of prognosis and a focal point of PAH treatment, hemodynamic parameters correlating with RV function and reserve, namely right atrial pressure (RAP), cardiac index (CI), and mixed venous oxygen saturation (SVO_2) are regarded as important independent prognostic factors in numerous studies. Current guidelines advise normalization of hemodynamics supporting greater RV stabilization rather than reversing the vascular disease process (ie, mean pulmonary artery pressure [mPAP] or pulmonary vascular resistance [PVR]). For instance, van de Veerdonk et al demonstrated that even when PAH therapies result in PVR reduction, patients may experience deterioration in RV ejection fraction (EF). Progressive RV dysfunction, irrespective of PVR change, assumes a more powerful role in prognostication than hemodynamics per se.[13]

The historical use of 6MWD as a primary endpoint for treatment efficacy and as a survival surrogate has long been accepted, although several questions remain about its validity and prognostic assumptions. Some believe that 6MWD with its many limitations lacks the sensitivity and clinical significance to detect changes in right heart function. The 6MWD has largely lacked predictive power because many of the individual clinical studies were not designed to evaluate mortality and survival.[14] It is furthermore uncertain whether absolute responder thresholds of 6MWD suggested as >380 m from Sitbon et al or >400 m associated with improved survival in REVEAL are as useful as relative improvements in 6MWD.[15,16]

A recent meta-analysis evaluating the results of 22 clinical trials concluded that favorable treatment effects linked to lower all-cause mortality, PAH hospitalization, transplant, and need for rescue therapy were not predicted by changes in 6MWD alone.[17] Improvement in the 6MWD of ≥41.8 m was evidently found to be the minimally important difference that correlated with lowered odds of a clinical event at 12 weeks, but this again accounted for only 22% of the treatment effect.[18] Thus, it seems that change in 6MWD is at best a modestly valid surrogate for clinical events. Additionally, clinical studies and clinicians heavily emphasize improvements in 6MWD to determine clinical response to treatment, but until recently have extracted less insight on the meaning of a deteriorating walk distance. Farber et al recently showed that worsening 6MWD, but not a stable or improving 6MWD, was strongly associated with survival and that a 15% reduction in 6MWD may be necessary for this observed effect.[14]

Despite the challenges of identifying novel noninvasive markers of disease, the study of biomarkers for diagnosis, pathogenesis, disease progression, and treatment guidance in PAH and RV dysfunction remains an active area of investigation. The many different pathobiological mechanisms involved in PAH have led to an explosion of disease-specific biomarkers (Table 1), but to date, none of these has demonstrated all the characteristics of the ideal biomarker.[19] Evidence suggests that a multiple biomarker approach may yield incrementally more information on disease state and prognosis rather than reliance on a single marker.

Of all the markers, brain natriuretic peptide (BNP) and its cleavage product, N-terminal prohormone BNP (NT-proBNP), are the most widely studied and clinically relevant markers for outcome prediction in current practice. B-type natriuretic peptide is elevated in a number of PH subtypes and correlates with acute and chronic hemodynamic derangements indicative of RV stress and

Table 1. Different pathophysiologic mechanisms and associated biomarkers

BIOMARKERS IN PAH				
Pathobiology	**Biomarker**	**Availability**	**Specificity**	**Prognostic Value**
Neurohormonal Activation	• Natriuretic peptides*	+++	−	+
	• Endothelin-1	+	−	+
	• Adrenomedullin	+	−	+
	• Copeptin	+	−	+
End organ failure	• Creatinine	+++	−	+
	• Sodium	+++	−	+
	• Uric acid	+++	−	+
Myocardial injury	• Troponin	+++	−	+
Inflammatory markers	• Interleukins	+++	−	+
	• C-reactive protein	+++	−	+
Vascular remodeling	• Von Willebrand factor	+	−	+
	• Angiopoietin	+	−	+
	• Growth differentiation factor	+	−	+
Genomics/Proteomics	• Unknown	−	+++	Unknown

*Only biomarker to date used in clinical practice and included in PH therapy-driven guidelines.

therapy responsiveness. It also acts as an independent predictor of mortality in PAH (eg, lower survival observed in patients with baseline BNP ≥150 pg/mL).[20] The BNP level is the only biomarker currently included as a potential treatment goal in PAH (Table 2). Rather than trying to achieve a "normal" BNP as current guidelines suggest, it may be more practical to individualize BNP values, taking into account the influence of age, sex, and renal function when trying to attain an individual's lowest possible BNP or NT-proBNP with titratable therapies. It remains to be seen whether natriuretic peptide-guided pharmacologic therapy can significantly reduce morbidity and mortality related to right-sided heart failure in PAH, as shown in patients with chronic left heart failure, and how this ranks compared to simultaneously important hemodynamic and imaging markers of RV function.

The study of biomarkers can advance the understanding of the complex disease pathways involved in PAH. Many studies promoting specific biomarkers are small, investigational, or hypothesis generating, lack rigorous validation, and may not adequately discriminate between high- and low-risk patients. Future biomarkers must have high sensitivity and specificity for the disease state, but must also overcome the limitations of the currently used markers (ie, invasiveness of catheterization and insufficient reproducibility of imaging) for increased utility. The proliferating data from ongoing biomarker studies must therefore be critically interpreted before biomarkers can affect current management in PAH.

TREATMENT GOALS AND CLINICAL RESPONSE USING MULTIPLE RISK PREDICTORS

No single risk parameter can satisfy the need for reliable long-term prognostication. Furthermore, we lack agreement on which parameter(s) carry the greatest weight and validity for directing therapy. Composite treatment goals are more meaningful and a strategy aimed at integrating hemodynamic, clinical, and RV imaging metrics; biomarker data; and treatment goals holds greater promise for outcome prediction. It is becoming clear that defining multiple goals of interest with absolute and relative thresholds or specific cut points to target with pharmacotherapy is crucial. It is also apparent that follow-up risk assessment is as, if not more, important than baseline evaluation. In a study of PAH patients by Nickel et al, those who attained World Health Organization (WHO) functional class (FC) I/II status, CI >2.5 L/min/m^2, SVO_2 ≥65%, and NT-proBNP <1800 pg/mL after targeted therapy did better than those who did not, irrespective of baseline risk status.[21] An integrative and individualized approach using multitiered parameters reflecting one's clinical response *over time* is likely to be more informative for outcome prediction and disease management.

Table 2. Variables Used in Clinical Practice to Determine Response to Therapy and Prognosis in PAH Patients

Functional Class I or II
Echocardiography/CMR Normal/near-normal RV size and function
Hemodynamics Normalization of RV function using RAP <8 mm Hg and CI >2.5-3.0 L/min/m^2
6MWD >380 to 440 m
Cardiopulmonary exercise testing Peak VO_2 >15 mL/min/kg and $EqCO_2$ <45 L/min
B-type natriuretic peptide level Normal

Adapted from McLaughlin VV et al.[22] CMR = cardiac magnetic resonance; RV = right ventricular; RAP = right atrial pressure; CI = cardiac index; 6MWD = 6-minute walk distance; VO_2 = peak oxygen consumption; $EqCO_2$= ventilator equivalent for carbon dioxide.

Current treatment guidelines recommend assessing multiple parameters for gauging the efficacy of a therapy. Updated treatment goals for PAH include: New York Heart Association FC I or II, 6MWD ≥380 to 440 m, cardiopulmonary exercise testing with peak oxygen consumption (VO_2) >15 mL/min/kg and ventilator equivalent for carbon dioxide <45 L/min, BNP levels approaching "normal," echocardiography or cardiac magnetic resonance imaging (CMR) revealing near-normal RV size and function, and RAP <8 mm Hg and CI >2.5 to 3.0 L/min/m^2, derived from previously published prognostic levels in PAH patients and the priority given to stabilizing RV function (Table 1).[22] More recently, riociguat-treated patients with PAH and with inoperable or persistent chronic thromboembolic pulmonary hypertension (CTEPH) in the PATENT-1 and CHEST-1 studies, respectively, were assessed against placebo controls for "positive response" to therapy, defined as ability to meet prespecified criteria.[23,24] In both studies, a positive responder threshold was defined as an increase in 6MWD ≤40 m, 6MWD ≤380 m, CI ≤2.5 L/min/m^2, WHO FC I/II, NT-proBNP <1800 pg/mL, and RAP <8 mm Hg. In the CHEST-1 study, an additional criterion of achieving PVR <500 dyn·sec·cm^{-5} was included because of its common use in CTEPH patients for prognostication. These studies assessed both individual responder endpoints and the combined responder endpoint, and concluded that riociguat increased the proportion of patients achieving this combined endpoint compared with a placebo group. In PATENT-1, treatment with riociguat after 12 weeks increased combined endpoint responsiveness from 15% at baseline to 34% of patients, but was largely unchanged in the placebo group. In CHEST-1, the proportion of patients meeting combined responder criteria increased from 5% to 25% after 16 weeks of treatment with riociguat, but again remained unchanged in the placebo arm. The odds ratio for achieving a combined responder endpoint with ricioguat compared to placebo was 4.98 (95% CI 1.68-14.77, P=0.0007). Although the proportion of patients achieving a combined endpoint was lower than the proportion achieving individual criteria in both of these studies, these analyses lend further support to using composite treatment goals over a range of individual responder variables for survival prediction.

REGISTRIES AND RISK SCORES

Modern-day registries have tremendously expanded our knowledge on the demographics, clinical and hemodynamic profiles of patients, and epidemiology and survival of contemporary PAH cohorts. From registry data, collective determinants of survival on multivariable analysis can be identified and used to create prognostic equations to predict survival at any point in a patient's disease course. The NIH registry was the first registry to evaluate survival and develop a prognostic model of untreated patients in 1981. Since that landmark study, 4 recent registries (French registry, PHC registry, Mayo Clinic registry, and—the largest of all—REVEAL registry) have introduced better discriminatory models that have shown improved survival with available PAH therapies. Each of these registries draw from varying numbers of patients, including both prevalent and incident cohorts, different observation periods, diverse PAH subgroups, and periods of survival, yet the key predictors of outcome are surprisingly congruent across the studies.[21,22] These include sex, FC, exercise capacity by 6MWD, and RAP and cardiac output (CO) as invariably powerful hemodynamic parameters in PAH. In fact, hemodynamic parameters were some of the first used for predicting outcome from the NIH registry, which derived its survival equation using RAP, CI, and mPAP as predetermined variables that were each independently predictive of death. Although risk models have limitations and require broader validation in different patient populations, the models offer a stronger framework for risk prediction than using single predictors of the disease.

Despite improved observed survival rates in modern-day PAH registries, it is important to acknowledge that survival in almost all registries, including REVEAL and the French registry, examined newly diagnosed *and* prevalent cases—the latter of which can introduce a survivor bias. Thus, generalizing results from registry data must take into account the population studied, time from symptom onset to diagnosis, biases in treatment access, and understanding of which patients the results can be applied to. For instance, survival estimates from the time of enrollment in a predominantly prevalent cohort can be misleading if then used to predict outcomes in newly diagnosed patients.[25] Furthermore, clinicians must understand the registry population, different inclusion and exclusion criteria, and epidemiology of PAH patients being studied to derive survival estimates, and whether applicable to the intended population or patient for whom risk prediction is desired.

Despite being derived in a combined prevalent and incident cohort at time of enrollment, the REVEAL PAH risk score equation maintained its predictive power and was validated in a separate cohort of newly diagnosed patients.[26] The REVEAL equation was also externally validated in matched patients from the French registry,[27] as well as in other distinct PH populations, and shown to have good discriminatory power to predict 1-year and 5-year survival.[28] More recently, the REVEAL model performed well for risk prediction in non-PAH patients, suggesting its potential for broader application in a more general PH population.[29] Recognizing that a vast majority of patients have non-PAH or multifactorial PH, future registry analyses should be directed at broadening to other PH groups, namely Group 2 and Group 3 PH. The advantage of doing so is to better understand the clinical course and how to approach this large, heterogeneous, at-risk population who presently do not qualify for traditional PH treatments.

The predictors of 1-year survival from patients enrolled in REVEAL were evaluated in a multivariate analysis to create a weighted risk formula to be used at any time in the disease course. The final

prognostic equation contains 19 predictive factors, each of which are independently predictive, and the equation has excellent discriminatory power (c-index 0.772) for distinguishing between patients who are likely to die vs those likely to survive.[30] Given a pair of randomly selected patients, one who dies and one who survives, the c-index is an estimate of the probability that the patient who died had a higher predicted chance of death (the closer the c-index is to 1.0, the better the model discriminates). The REVEAL equation has greater discriminatory ability in contrast, for instance, to the NIH equation, which incorporated 3 hemodynamic variables a priori (c-index 0.588), and to the French registry, which yielded 3 variables as well (sex, CO, 6MWD) on multivariable analysis significantly associated with survival (c-index 0.57). No c-index was calculated for the PHC equation. It is possible that REVEAL's superior discriminatory ability is due to an inclusion of multiple covariates, which was preserved even when patients lacked or were missing some of the predictive factors in the equation (the average patient in REVEAL had data only for 16 of the 19 factors).

In contrast to the French registry equation, which is not intended to predict individual patient outcomes but rather is used for survival comparison in other PAH cohorts, the REVEAL equation has been transformed and validated into a risk calculator that provides a numerical value for the risk score that can be used clinically for the individual patient at diagnosis and in serial follow-up (Figure 2). Five risk strata based on risk scores have been developed and are shown in Figure 3. REVEAL can even be used when missing variables, without sacrificing the significant predictive power of the equation as shown by Cogswell et al.[31] This analysis selectively removed the right heart catheterization and pulmonary function testing data, specifically a PVR ≤32 Wood units or diffusion lung capacity for carbon monoxide '32%, which represent extremes not met in a majority of patients, and may explain why this model performed nearly identically to the full original REVEAL model

Figure 2: Reprinted with permission from Benza et al.[26] Calculated risk scores can range from 0 (lowest risk) to 22 (highest risk). If NT-proBNP is available and BNP is not, listed cut points are replaced with <300 pg/mL and >1500 pg/mL. APAH = associated pulmonary arterial hypertension; BNP = brain natriuretic peptide; BPM = beats per minute; CTD = connective tissue disease; DLco = diffusing capacity of lung for carbon monoxide; FPAH = familial pulmonary arterial hypertension; HR = heart rate; mRAP = mean right atrial pressure; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PoPH = portopulmonary hypertension; PVR = pulmonary vascular resistance; REVEAL = Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; SBP = systolic BP; WHO = World Health Organization. Reproduced with permission from the American College of Chest Physicians. Benza RL, Gomberg-Maitland M, Miller DP, et al. The REVEAL Registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. *Chest.* 2012; 141(2):354-362.

(c-index 0.759 compared with full REVEAL 0.765, P=0.92). The analysis also modified the full REVEAL model to include only noninvasive variables of the PAH WHO diagnostic group, WHO FC, BNP, renal function, and RAP by echocardiogram and found comparable 1-year survival discrimination with the full model. The preservation of this model perhaps suggests these are the most salient predictors and best suited for long-term disease monitoring. This further highlights that a more simplified use of the REVEAL score may be appropriate, clinically advantageous with broader applicability, and accurate even when clinicians lack some of the variables at diagnosis and follow-up.

Because all variable data are rarely captured at a single point in time due to the reality of clinical practice, the calculator allows for entry any time a new variable becomes available or is reassessed. One major limitation of this, however, is that a patient's measured health state using the risk calculator at disparate points in time may not accurately signal the current disease state,

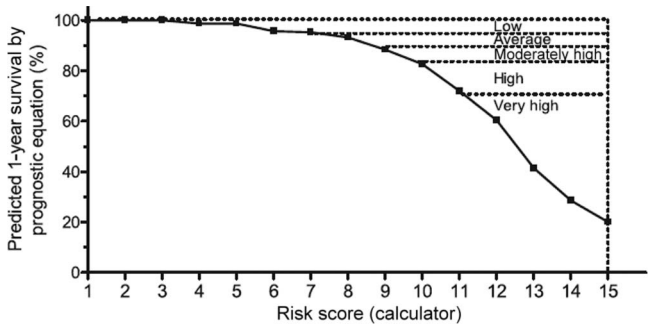

Figure 3: One-year Kaplan-Meier survival estimate for the REVEAL development cohort using predicted risk scores. Adapted with permission from Benza et al.[26] One-year survival for low-risk group (risk score 1–7): 95%–100%; average-risk group (risk score 8): 90%–<95%; moderately high-risk group (risk score 9): 85%–<90%; high-risk group (risk scores 10–11): 70%–<85%; very high-risk group (risk score ≤12): <70%. Reproduced with permission from the American College of Chest Physicians. Benza RL, Gomberg-Maitland M, Miller DP, et al. The REVEAL Registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. *Chest.* 2012;141(2):354-362.

especially when predictors change with alternating periods of decompensation and clinical stabilization. For instance, if a BNP rises from 200 pg/mL to 400 pg/mL, this will not worsen the REVEAL risk score because both values are above the threshold of risk, despite the prognostic significance of a doubling in biomarker value. Similarly, a 15% decline in 6MWD, as described earlier, signals higher risk of disease progression than an absolute maintained distance >165 m. Ideally, a risk model should have the sensitivity to detect the dynamic nature of the disease, with changes in the positive or negative direction around cut points, and determine if such changes are clinically relevant and influential for guiding therapy. An additional consideration when devising or improving risk scores is to consider the weight of nonmodifiable variables (ie, sex or PAH subgroup) and modifiable variables (ie, hemodynamic parameters) differently, as nonmodifiable variables may undermine positive changes in other variables and temper the gains in the risk score. Efforts to improve a patient's risk score over time, and hence survival, could thus seem futile if risk scores do not adjust accordingly to overcome constant patient factors.

To explore its serial utility, Benza et al recently reevaluated the REVEAL score to determine whether repeat assessments are valid and convey important prognostic information after adjusting for risk at enrollment.[5] This analysis evaluated subsequent 1-year survival for patients based on an increased, decreased, or unchanged risk score during the initial 12 months of follow-up from enrollment. The risk score was calculated at enrollment in REVEAL and recalculated again at 12 months, replacing any component of the risk score that had been reevaluated during that 12-month period. At the time of recalculation, 38% of patients had no change in risk score, 32% had improved risk scores by at least 1 point, and 30% had a worsening risk score by at least 1 point. Not surprisingly, newly diagnosed patients had improved scores compared with prevalent patients (41% compared with 28%, respectively) due to the initiation of PAH therapies in a majority of new patients (67%) during that first year. A worsened risk score significantly predicted subsequent 1-year survival, with a hazard ratio (HR) 1.67 (95% CI, 1.41-1.99, $P<0.001$), and an improved risk score was associated with a HR of 0.57 (95% CI, 0.47-0.69, $P<0.001$). When follow-up risk scores were compared to enrollment risk score, the value at reassessment was a much stronger predictor of survival than the baseline determination. Nonetheless, the baseline risk score maintained a significant effect on future survival. Importantly, the changes in risk score were not explained by any single parameter predominantly, again underscoring that multifactorial risk components are best for survival prediction. This study demonstrated the prognostic value of using the REVEAL equation and risk score calculator in a serial fashion, to support clinicians in identifying patients with stable, improving, or progressive pulmonary vascular disease through regular risk modeling. In this manner, REVEAL and future risk models may enhance the individualized patient approach and actively inform treatment goals and guide timing of interventions.

FUTURE DIRECTIONS USING PROGNOSTIC TOOLS

Presently, risk scores are not utilized as endpoints for clinical trials, and there is more to be done to characterize the prognostic effects of treatment in an aggregate model. For instance, it is understood that a patient initiated on intravenous prostacyclin has a disease trajectory different from one not yet on prostacyclin, despite the 2 possibly having identical REVEAL risk scores for different reasons. Before risk scores can be utilized for clinical response outcomes or encouraging a goal-oriented therapy approach, we have to first interpret treatment effect on risk scores for the study period or over a patient's lifetime. If we use the Seattle Heart Failure Model as an example of individual risk prediction in a broad heart failure population, this model permits mortality projections to change based on addition or withdrawal of evidence-based therapies, and can predict mode of death such as pump failure or sudden cardiac death.[32] It is important to recognize that unlike heart failure, the field of PAH lacks robust evidence-based data for a majority of therapies, thus explaining the challenge of integrating drug interventions in current models. For instance, we do not fully know the relative risks of single vs combination therapy vs parenteral therapy, and whether particular drug selection affects survival or is simply a signal for disease severity. Until we better understand the relative risks or benefits of the available therapies, it will be challenging to derive models that change according to a chosen drug strategy.

In the future, we should elect to design risk models that enable selection of therapies while considering patient preference, include advanced options and

newer device-based therapies, provide realistic projections for the individual patient and family, and more precisely define those factors that are important for disease management. In the last 10 years, the focus on improvement and/or preservation of RV function has increased. The study of RV pathology in PAH has become more sophisticated to potentially allow inclusion of novel RV specific factors (ie, RV strain, RV-PA coupling, RV responsiveness to stress or exercise) in future models. An "RV-centric" strategy may be the essential link for stronger modeling and disease prediction. Identification of newer disease-modifying targets and study of broader phenotypes will be necessary to improve existing tools and positively affect the care of PH patients.

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